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Coadministration of albumin and furosemide in patients with the nephrotic syndrome

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Background. In patients with nephrotic syndrome, the natriuretic effect of furosemide (FU) is diminished. The effect of coadministration of FU and human albumin (HA) has remained controversial.

Methods. In a double-blind, placebo-controlled study, nine nephrotic patients (six males, 48 ± 4 years) on standardized sodium chloride intake, in random order on three separate days, received by intravenous administration for 60 minutes either (*a*) 60 mg FU plus a sham infusion, (*b*) 60 mg FU plus 200 ml of a 20% solution of HA, or (*c*) sham infusion plus 200 ml of a 20% solution of HA. Urinary volume, sodium, albumin and FU excretion, renal hemodynamics, and plasma atrial natriuretic factor concentration were assessed.

Results. Administration of FU alone significantly ($P < 0.01$) increased mean cumulative urinary sodium (259 ± 30 mmol) and volume excretion (2684 ± 167 ml) in the first eight hours as compared with the HA infusion alone (118 ± 12 mmol, 1827 ± 141 ml). The coadministration of FU and HA caused an even more marked increase ($P < 0.01$ vs. HA alone) of urinary sodium (312 ± 28 mmol) and volume excretion (3230 ± 201 ml); the difference to FU administration alone was significant ($P < 0.05$). Plasma atrial natriuretic factor, serum albumin concentration, and urinary albumin excretion increased significantly on both HA infusion days, whereas urinary excretion of FU remained unchanged with HA coadministration. Glomerular filtration rate (C_{In}) was not significantly affected by any of the infusion protocols, but effective renal plasma flow (C_{PAH}) increased significantly on both HA infusion days.

Conclusions. Coadministration of HA potentiates the action of FU in patients with the nephrotic syndrome, but only modestly. This effect is mediated by changes in renal hemodynamics.

In patients with the nephrotic syndrome, the natriuretic effect of furosemide (FU) is thought to be diminished for pharmacokinetic and pharmacodynamic reasons [1–6]. Increased doses of FU alone or FU in combination with a thiazide diuretic to block distal tubular reabsorption are recommended to overcome the hyporesponsiveness to FU [7].

Furosemide, like other loop diuretics, is bound to plasma protein, mainly albumin. The albumin-bound fraction of FU reaches the abluminal site of the proximal tubular epithelial cells and interacts with the anion transporter so that FU is translocated into the tubular lumen. Hypoalbuminemia diminishes the amount of albumin-bound FU that can interact with the anion transporter and, in consequence, diminishes the FU delivery to its site of action, that is, the ascending limb of the loop of Henle [1, 6]. Coadministration of FU with intravenous albumin could theoretically improve delivery and the natriuretic effect of FU, that is, change the pharmacokinetics of FU. This approach has been shown to restore the natriuretic action of FU in analbuminemic nephrotic rats [3]. In addition, albumin infusion may increase the natriuretic effect of FU via other mechanisms, including reversal of absolute or relative hypovolemia, and transient reversal of sodium-conserving neural or humoral mechanisms. In view of the many potential mechanisms, it is not surprising that in humans the effect of coadministration is controversial [4, 8–12]. The reasons for the variability of results may include differences in volume status, renal function, type of disease causing the nephrotic syndrome, etc. [13, 14].

This double-blind, randomized, placebo-controlled cross-over study was designed to compare the diuretic and natriuretic effects of intravenous FU in combination with an infusion of human albumin (HA) or a sham infusion. Nine patients with nephrotic syndrome who were on a controlled intake of sodium chloride were examined. Complete simultaneous assessment of accessible factors influencing natriuresis was attempted under controlled conditions.

Key words: atrial natriuretic factor, natriuresis, distal tubular reabsorption, loop diuretic, glomerulonephritis, renal hemodynamics.

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METHODS

Patients

All consecutive patients who agreed to participate (by written informed consent) and who met the entry criteria were included into the study. Entry criteria included: urinary protein excretion above 3.5 g/24 hr (that is, nephrotic range proteinuria), primary renal disease (the absence of amyloidosis or other systemic diseases), and a defined glomerular histology to minimize the heterogeneity of underlying conditions (6 patients had biopsy-proven membranous glomerulonephritis and 3 minimal change glomerulonephritis/focal-segmental glomerulosclerosis). Routine blood chemistry and urine analysis were performed at entry into the study. Nine patients were studied (6 males, mean age 48 ± 4 years; BMI 26.6 ± 1.6 kg/m^2). Their mean 24-hour protein excretion in the screening phase was 12.3 ± 1.3 g/24 hr, mean serum protein concentration 52 ± 3 g/liter, and mean arterial blood pressure (MAP) 100 ± 2 mm Hg. In all but one patient, the renal function was within the normal range (serum creatinine concentration below 1.3 mg/dl) and the mean glomerular filtration rate (GFR) was 105 ± 9 ml/min/1.73 m^2. All patients had been on diuretic medication, and this was withdrawn for at least one week prior to the start of the study. At study entry, moderate (++) to marked (+++) edema was present in all patients. Antihypertensive drugs (if present) were not washed out, but their dosage was kept unchanged throughout the study.

Protocol

The protocol of this study was approved by the Ethics Committee of the University of Heidelberg. A double-blind, placebo-controlled cross-over design was used. For 10 days, patients adhered to a diet containing a standardized amount of sodium chloride. The diet was prepared as precooked, deep-frozen meals with a standardized sodium content of 20 mmol/day (low-salt diet). To achieve a final daily sodium intake of approximately 80 mmol, the diet was supplemented with six slow-release salt tablets (Ciba-Geigy, London, UK), each containing 10 mmol of sodium. Dietary compliance was controlled by regular measurements of 24-hour urinary sodium excretion. In addition, patients were instructed to keep their daily fluid intake constant, that is, to drink approximately 2 liters of tap water. They were also advised to refrain from taking a sauna, doing any sporting activity or unaccustomed physical exertion for the period of the study. On the fifth, seventh, and ninth study days, patients were given in random order the following infusions: (*a*) 60 mg of FU (Lasix®; Hoechst AG, Frankfurt, Germany) dissolved in 50 ml of a 0.9% NaCl solution, plus a sham infusion (200 ml of aqua ad iniectabilia), (*b*) 60 mg of FU dissolved in 50 ml of a 0.9% NaCl solution plus 200 ml of a 20% solution of HA (Normal-Serum-Albumin Alpha 20%®; Alpha Therapeutic GmbH, Langen, Germany), and (*c*) a sham infusion (50 ml of a 0.9% NaCl solution) plus 200 ml of a 20% solution of HA. The patients were allocated to the different treatment sequences using random numbers. The intravenous route of FU administration was chosen to avoid potential interference with intestinal absorption. The dose of 40 g of HA (200 ml of a 20% solution) was chosen in order to avoid a supranormal oncotic pressure [15].

Patients were examined in a quiet environment while in a recumbent position. They fasted during the first 10 hours (from 8 a.m. to 6 p.m.); afterward, they were up and about. The infusions mentioned earlier here were given at 10 a.m. over a period of 60 minutes. Mean arterial pressure (MAP) was measured at regular intervals before drug administration and thereafter. The patients collected urine over 24 hours, from 8 a.m. to 10 a.m., from 10 a.m. to 12 a.m., from 12 a.m. to 2 p.m., from 2 p.m. to 4 p.m., from 4 p.m. to 6 p.m., and from 6 p.m. to 8 a.m. of the next day. Urinary sodium, albumin, and FU excretions were assessed in the urine samples. To achieve a steady state of urine flow, patients drank a quantity of tap water that matched the urine volume passed in the preceding period. GFR and effective renal plasma flow were assessed using the inulin (C_{In}) and paraaminohippurate (C_{PAH}) clearance methods as described elsewhere [16]. In brief, a priming dose of 1500 mg inulin/m^2 (Inutest®; Laevosan Co., Linz, Austria) and 500 mg PAH/m^2 (Nephrotest®; Biologische Arbeitsgemeinschaft GmbH, Lich, Germany) was given at 8 a.m. The bolus injection was followed by continuous infusions of inulin (10 mg/m^2/min) and PAH (8 mg/m^2/min) maintained with ultraprecise pumps (Perfusor FT®; Braun Melsungen, Melsungen, Germany) from 8 a.m. to 6 p.m. Both the bolus injection and the continuous infusions of inulin and PAH were administered in 0.9% NaCl solution. The amount of sodium chloride administered with the infusions was identical on all study days. After a 120-minute equilibration period (from 8 a.m. to 10 a.m.), blood samples for measurements of GFR and effective renal plasma flow were withdrawn at regular intervals until 6 p.m. In addition, blood samples for the measurement of atrial natriuretic factor (ANF) and serum albumin concentration were withdrawn at 10 a.m., 12 a.m., and 4 p.m. Body weight was measured on all study days.

Measurements and calculations

Plasma and urine sodium concentrations were measured with flame photometry (Eppendorf 5051®; Hamburg, Germany), and serum and urine albumin concentrations with nephelometry (Array Protein System®; Beckmann Instruments, Munich, Germany). Plasma concentration of ANF was measured with radioimmunoassay, the concentration of FU in urine with fluorometry and high-performance liquid chromatography. Urine samples were collected in light-protected tubes because

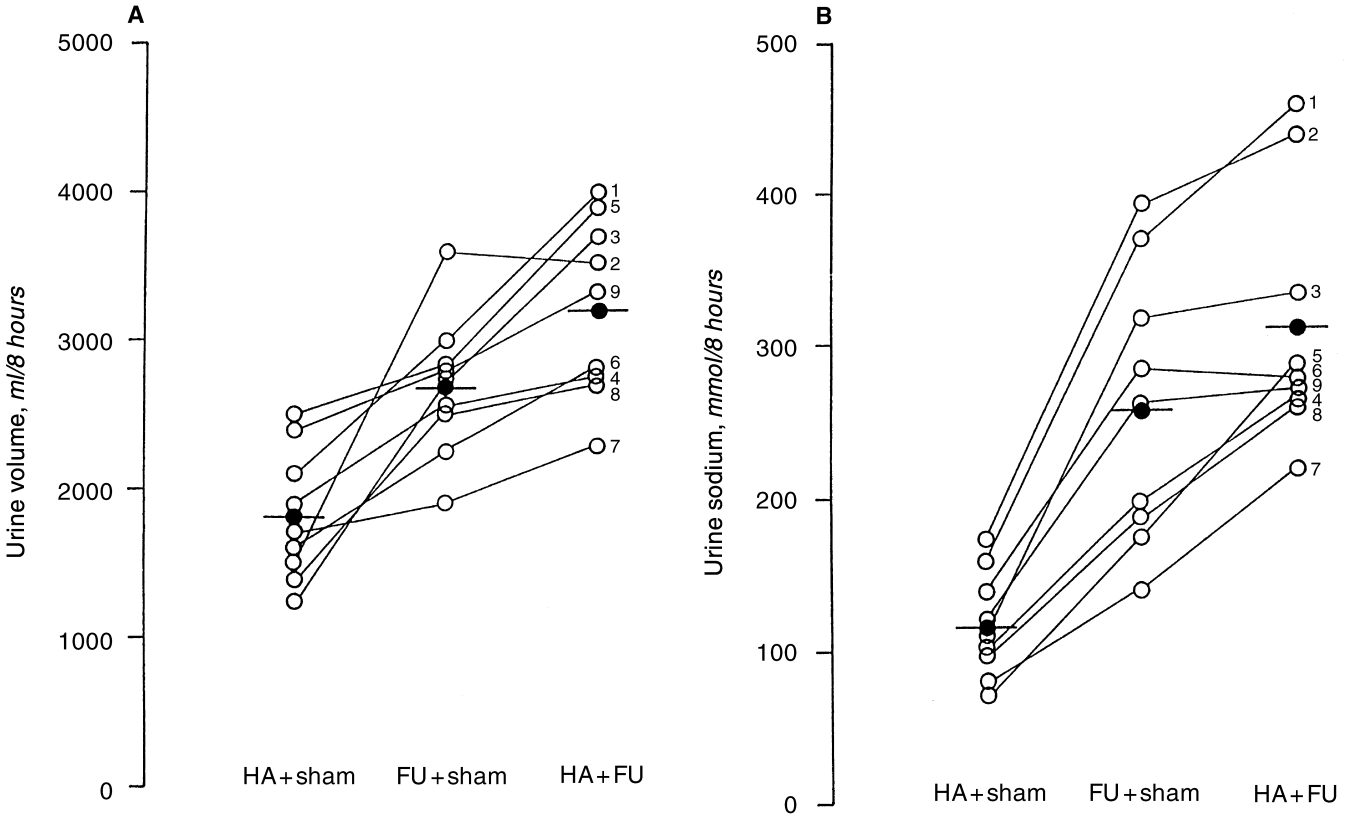

Fig. 1. Individual data on urinary volume (*A*) and sodium (*B*) excretion in nine patients with nephrotic syndrome during the first eight hours after infusion of human albumin plus sham infusion (HA + sham), infusion of furosemide plus sham infusion (FU + sham), or infusion of furosemide plus human albumin (FU + HA). Symbols are: (○) individual data; (●) mean value. The underlying renal disease and 24-hour urinary protein excretion on study entry in our patients were as follows: patient 1, FSGS/5.4 g; patient 2, MGN/14.7 g; patient 3, FSGS/17.8 g; patient 4, MGN/12.2 g; patient 5, MGN/12.8 g; patient 6, FSGS/12.0 g; patient 7, MGN/4.5 g; patient 8, MGN/11.9 g; patient 9, MGN/12.5 g. Abbreviations are: FSGS, minimal change glomerulonephritis/focal-segmental glomerulosclerosis; MGN, membranous glomerulonephritis.

of the known photosensitivity of FU. Inulin was determined enzymatically using inulinase [17] and paraaminohippurate after the method of Braton-Marshall [18]. C_{In} and C_{PAH} were calculated from the delivered dose:

$$C = (Ir \times Ic)/Sc$$

where C is the clearance, Ir is the infusion rate (ml/min), Ic is the concentration of the analyte in the infusion fluid (mg/ml), and Sc is the serum concentration of the analyte (mg/ml). MAP was measured oscillometrically using an automatic blood pressure-monitoring device (Dinamap®; Critikon Co., Tampa, FL, USA).

Table 1. Mean cumulative urinary volume (UV), sodium (U_{Na}), chloride (U_{Cl}) and albumin (U_{Alb}) excretion in 9 patients with nephrotic syndrome during the first 8 hours after infusion of human albumin plus sham administration (HA + sham), administration of furosemide plus infusion (FU + sham) or administration of furosemide plus human albumin (FU + HA)

	HA + sham	FU + sham	FU + HA
UV *ml/8 hr*	1827 ± 141[a]	2684 ± 167[d]	3230 ± 201[b]
U_{Na} *mmol/8 hr*	118 ± 12[a]	259 ± 30[c]	312 ± 28[b]
U_{Cl} *mmol/8 hr*	105 ± 11[a]	231 ± 31[c]	283 ± 28[b]
U_{Alb} *mg/8 hr*	2641 ± 538[a]	1601 ± 323[d]	2709 ± 508

[a] $P < 0.01$, HA + sham vs. FU + sham
[b] $P < 0.01$, HA + sham vs. FU + HA
[c] $P < 0.05$ and [d] $P < 0.01$, FU + sham vs. FU + HA

Statistics

The predetermined primary efficacy parameters were the differences of mean urinary sodium and volume excretions in the first eight hours after the start of infusions between the following protocols: (*a*) administration of FU plus sham infusion, (*b*) administration of FU plus infusion of HA, and (*c*) sham administration plus infusion of HA. Data were evaluated with the SPSS program using the Friedman test, that is, a nonparametric test for multiple comparisons of related data. If this test gave a significant difference between treatments, a two-sided Wilcoxon test for paired data was applied to compare the respective treatments. Other parameters were compared using the previously mentioned tests. Differences were accepted as statistically significant at a P level of 0.05. Data are shown as mean ± SEM.

RESULTS

Furosemide alone significantly increased cumulative sodium, chloride, and volume excretion as compared with the infusion of HA alone (Table 1). Coadministration of FU and HA caused an even more marked increase of cumulative sodium, chloride, and volume excretion. The difference between FU plus HA versus FU plus sham infusion was modest but significant. Figure 1 shows individual data on volume and sodium excretion in patients during the first eight hours after administration of respective infusions. Coadministration of FU and HA was more effective even with respect to cumulative 24-hour sodium and volume excretion (374 ± 34 mmol, 4280 ± 184 ml) as compared with FU administration alone (304 ± 34 ml, 3777 ± 159 mmol) and with infusion of HA alone (193 ± 13 mmol, 2867 ± 176 ml).

An increase of mean plasma ANF and serum albumin concentration was observed on both days with HA infusion, whereas MAP did not differ significantly between the three infusion protocols (Table 2). In parallel, GFR was unchanged, but effective renal plasma flow increased on both HA infusion days. There was no significant difference in urinary FU excretion in the first eight hours when FU was administered alone as compared with coadministration of FU and HA. The cumulative urinary FU excretions with infusion of FU plus sham infusion as compared with FU plus HA infusion were similar at two hours (23.1 ± 3.6 vs. 24.0 ± 3.8 mg), four hours (32.0 ± 3.9 vs. 32.3 ± 4.4 mg), six hours (34.3 ± 3.8 vs. 34.4 ± 4.2 mg) and eight hours (34.9 ± 3.7 vs. 35.1 ± 4.2 mg). In contrast, mean urinary albumin excretion increased significantly with the administration of HA (Table 1).

The patients lost on average a total of approximately 500 mmol sodium during the six-day study period (that is, urinary sodium excretion minus dietary intake plus sodium infused on the study days). Because of the randomization of our patients to the different treatments, the mean 24-hour sodium excretion in the days after the studies was similar with all treatments (82 ± 11 mmol, HA + sham; 83 ± 12 mmol, FU + sham; and 80 ± 14 mmol, FU + HA). The same was true for mean 24-hour urinary volume excretion (2098 ± 351 ml, HA + sham; 1968 ± 374 ml, FU + sham; and 1953 ± 387 ml, FU + HA), the mean patient body weight (78 ± 6 kg, HA + sham; 78 ± 6 kg, FU + sham; and 78 ± 6 kg, FU + HA), as well as the average MAP (at 10 a.m. of the three study days; 100 ± 2 mm Hg, FU + HA; 103 ± 2 mm Hg, FU + sham; and 99 ± 2 mm Hg, HA + sham). As a consequence of the modest cumulative sodium loss during the six-day study period, the mean plasma sodium concentration in our nine patients decreased from 141 ± 1 to 135 ± 1 mmol/liter, and body weight decreased from 79 ± 6 to 76 ± 6 kg from study day 5 to study day 10. Table 3 gives individual data on infusions administered, body weight, blood pressure, and plasma sodium concentration on study days 5, 7, and 9.

Table 2. Plasma atrial natriuretic factor and serum albumin concentration, blood pressure and renal hemodynamics in 9 patients with nephrotic syndrome before (10 a.m.), as well as two hours (12 a.m.) and 6 hours (4 p.m.) after administration of various infusions

	10 a.m.	12 a.m.	4 p.m.
Infusion of human albumin plus sham infusion			
ANF *fmol/liter*	23.4 ± 3.4[b]	35.0 ± 4.3	29.6 ± 5.3
Serum albumin *g/liter*	29.9 ± 2.3[b]	38.0 ± 1.6	37.7 ± 1.5[d]
MAP *mm Hg*	97 ± 3	99 ± 3	98 ± 3
GFR *ml/min/1.73 m²*	107 ± 7	108 ± 8	105 ± 9
ERPF *ml/min/1.73 m²*	585 ± 46[b]	712 ± 61[e]	626 ± 53[c]
Infusion of furosemide plus sham infusion			
ANF *fmol/liter*	26.4 ± 4.8	21.9 ± 4.4	25.7 ± 4.3
Serum albumin *g/liter*	29.8 ± 2.3	30.9 ± 2.4	29.8 ± 2.3
MAP *mm Hg*	102 ± 4	105 ± 2	99 ± 2
GFR *ml/min/1.73 m²*	105 ± 7	108 ± 8	108 ± 9
ERPF *ml/min/1.73 m²*	576 ± 50	545 ± 35	550 ± 37
Infusion of human albumin plus furosemide infusion			
ANF *fmol/liter*	25.1 ± 3.9[a]	37.0 ± 4.1	32.6 ± 4.7[c]
Serum albumin *g/liter*	29.4 ± 2.6[b]	39.3 ± 2.5	37.5 ± 2.5[d]
MAP *mm Hg*	100 ± 3	102 ± 4	100 ± 3
GFR *ml/min/1.73 m²*	105 ± 7	106 ± 9	105 ± 9
ERPF *ml/min/1.73 m²*	581 ± 41[b]	732 ± 51[e]	592 ± 46

Abbreviations are: ANF – atrial natriuretic factor, MAP – mean arterial blood pressure, GFR – glomerular filtration rate by inulin clearance, ERPF – effective renal plasma flow by PAH-clearance.

[a] $P < 0.05$ and [b] $P < 0.01$, 10 a.m. vs. 12 a.m.

[c] $P < 0.05$ and [d] $P < 0.01$, 10 a.m. vs. 4 p.m.

[e] $P < 0.01$ – 12 a.m. vs. 4 p.m.

DISCUSSION

This study in patients with the nephrotic syndrome documents a modest but significant increase in urinary volume and sodium chloride excretion when HA was coadministered with FU as compared with administration of a submaximal dose of FU alone. Furthermore, the study identifies some mechanisms underlying the stimulatory effect of albumin coadministration on natriuresis, that is, volume expansion (as documented by an increase of plasma ANF concentration) with a concomitant increase in renal plasma flow. We admit that we did not measure PAH extraction; we cannot definitely exclude, but consider it unlikely, that there was a change in PAH extraction with no change in renal plasma flow. Our findings are compatible with the view that the effect of albumin is mainly mediated via a change in intrarenal hemodynamics. A direct effect of increased ANF concentrations on tubular sodium reabsorption after albumin infusion, as suggested by some studies [19, 20], is less plausible because most studies found resistance to the action of ANF in the nephrotic syndrome [13].

The assumption that intrarenal mechanisms are mainly responsible for the greater natriuretic response to albumin coadministration is further corroborated by the observation that albumin coadministration did not change the pattern of urinary FU excretion with time and the

Table 3. Individual data on randomization, body weight, blood pressure and plasma sodium concentration on 5th, 7th and 9th study day in 9 patients with nephrotic syndrome

Patient	5th day	7th day	9th day
1	FU + sham (57.8/102/142)	HA + FU (57.2/99/140)	HA + sham (56.1/99/136)
2	HA + FU (114.8/95/144)	FU + sham (111.8/91/139)	HA + sham (110.8/91/137)
3	HA + FU (80.1/99/140)	HA + sham (77.7/101/137)	FU + sham (77.5/106/136)
4	HA + sham (95.3/100/138)	FU + sham (94.5/102/137)	HA + FU (93.1/98/135)
5	HA + sham (56.1/106/141)	HA + FU (55.9/110/140)	FU + sham (55.0/109/136)
6	HA + sham (86.4/89/139)	HA + FU (86.2/92/138)	FU + sham (85.9/95/134)
7	FU + sham (79.5/107/142)	HA + sham (78.5/99/140)	HA + FU (78.3/100/139)
8	FU + sham (63.1/110/141)	HA + sham (61.7/112/138)	HA + FU (61.1/110/138)
9	HA + FU (79.5/101/143)	FU + sham (78.4/99/138)	HA + sham (78.1/102/136)

HA + sham is defined as infusion of human albumin plus sham administration; FU + sham, administration of furosemide plus sham infusion; and HA + FU is administration of furosemide plus human albumin. In brackets in consecutive order are: body weight in kg, mean arterial blood pressure in mm Hg and plasma sodium concentration in mmol/liter.

cumulative urinary FU excretion at eight hours in these moderately hypoproteinemic patients. Although the experiments of Inoue et al suggested the possibility that albumin infusion might increase FU delivery into tubular urine [3], we conclude that in our study conditions the albumin infusion does not alter the pharmacokinetics but definitely affects the pharmacodynamics of FU. We cannot exclude, however, that the amount of unbound (pharmacologically active) FU measured in the urine does not correspond to the active (unbound) FU at its site of action [5].

It was our intention to assess the mechanisms underlying the potentially higher efficacy of combination treatment in order to provide rational guidelines for the treatment of therapy-resistant nephrotic syndrome. This intention precluded the investigation of severely morbid patients, who cannot be maintained in a stable condition without permanent administration of diuretics, and the diuretics affect the steady state because of rebound phenomenon, fluctuations in volume status, etc. Consequently, our findings cannot necessarily be extrapolated to patients with more extreme degrees of nephrotic syndrome and hypoalbuminemia. We emphasize, however, that coadministration of FU and albumin caused a larger diuresis and natriuresis than FU alone, even in the patient with the highest urinary protein excretion (17.8 g/day) and the lowest serum albumin concentration (18.1 g/liter; Fig. 1). Because we did not have a fourth study arm with sham infusion for FU and sham infusion for albumin, the issue of whether the effect of albumin and FU was additive or even interactive cannot be addressed. A modestly negative sodium balance was observed in our patients during the six-day study period. We emphasize, however, that the randomized assignment to different treatment arms should have eliminated any systematic change related to differences in total sodium stores.

We observed no side effects. It is of note that in our patients, blood pressure did not increase after infusion of albumin despite an increase in blood volume after infusion of albumin, as documented by increased ANF concentrations. This is in line with previous observations, which documented that nephrotic patients can accommodate substantial volume loads without an increase in blood pressure [21]. It therefore seems relatively safe to administer albumin even in severely nephrotic patients.

How do our results compare with other controlled studies concerning the administration of albumin plus FU in patients with nephrotic syndrome? Previous studies did not provide measurements of ANF [4, 11] or renal clearances [11]. The patients studied were also heterogeneous with respect to the underlying renal disease, and in addition, most of these patients had impaired renal function. Sjöström et al administered 40 mg of FU and found an increase of cumulative sodium excretion of approximately 15% with infusion of either albumin or the volume expander dextran [4]; patients given albumin or dextran excreted exactly the amount of NaCl that had been administered. In contrast, Akcicek et al administered 1 mg FU per minute, that is, a maximal dose, to severely edematous nephrotic patients [11]. They failed to see a further increase of sodium excretion with coadministration of 0.5 g albumin/kg. It is notable that this FU dose had increased sodium excretion from 15 to 934 μmol/min, which is a substantial proportion of the filtered load. It would have been difficult to achieve any further increment.

As to the clinical management of patients with nephrotic syndrome, it emerges from our study, as well as two others [4, 11], that it is more sensible to increase the dose of FU than to infuse albumin. Our findings lend credence to numerous uncontrolled clinical observations that coadministration of albumin increases the natriuretic potency of FU at least at submaximal doses [8–10], but does not directly address the issue of whether the same is still true at maximal doses of FU. A potential drawback of this approach (besides the cost) is the short duration of albumin's action, as the increase in urinary volume and sodium excretion with the combination treatment compared with FU monotherapy was noted

in only the first eight hours after administration; this has also been noted in other studies [4].

In conclusion, coadministration of HA increases the natriuretic action of FU in patients with the nephrotic syndrome. The effect appears to be mainly mediated by changes in renal hemodynamics.

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